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Excess of Congenital Abnormalities in French-Canadian Children With Neuroblastoma: A Case Series Study From Montréal

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Neuroblastoma is one of the most common cancers of childhood. Some studies have shown an excess of congenital abnormalities in children who have been diagnosed with neuroblastoma. In this study we examined the medical records of all children with neuroblastoma seen at St. Justine Children's Hospital between the years 1977 and 1993. A total of 141 children (131 of French-Canadian ancestry) were included in this study. Twelve children (8.5%) had 21 defined congenital abnormalities (1,490 per 10,000 children). This compared with a rate of 444.3 children with abnormalities per 10,000 live births (4.44%) for all congenital abnormalities in the British Columbia Health Surveillance Registry, 1979–1988 (relative risk = 1.91, $P = 0.03$). Six of the 12 children had cardiovascular malformations. These and previous results suggest that there may be a common developmental origin to neuroblastoma and to some congenital malformations. Genes that control development may be worthy of further study in these children. Med. Pediatr. Oncol. 29:272–279, 1997. © 1997 Wiley-Liss, Inc.

Key words: neuroblastoma; congenital abnormalities; congenital heart disease; ribs

INTRODUCTION: NEUROBLASTOMA AND CONGENITAL MALFORMATIONS?

Neuroblastoma accounts for 8–10% of all childhood cancer, with ~550 new cases per year in the United States. The average age of diagnosis is 22 months [1]. It has been suggested that the occurrence of neuroblastoma, like retinoblastoma, can be explained by mutations in tumour suppressor genes [2]. However, unlike retinoblastoma, familial neuroblastoma is exceptionally uncommon, and it has been estimated that the inherited fraction of neuroblastoma is at most 1% [3]. Interestingly, there are several reports of the association of neuroblastoma with congenital abnormalities, such as cardiovascular and skeletal, particularly rib, malformations [4–9]. In support of these findings, some studies have shown that congenital malformations are significantly more common in children with neuroblastoma, and vice versa [5,10–12]. However, others have found either a nonsignificant increase or no increase in malformations in childhood neuroblastoma [13–17]. We therefore conducted a study of all children with neuroblastoma seen at one Montréal pediatric teaching hospital between the years of 1977 and 1993 to determine whether a relationship between congenital malformations and neuroblastoma exists in the Québec population.

MATERIALS AND METHODS

Chart Review

The charts of all children diagnosed with neuroblastoma between the years 1977–1993 at St. Justine Hospital for children, Montréal, Canada, were reviewed by one person (P.B.). A record was made for all children of the name and sex, status (alive/dead at time of chart review), date of birth and age of diagnosis, site of tumor, tumor stage and site of any metastases, ethnic group, and any congenital anomalies (Table I). Details of gestational age, age of parents, presence of twinning, and any disorders reported in the parents or other family members were also recorded, but information on these variables was not available for all children. All cases were pathologically confirmed. No affected children or their family members were contacted, and no attempt was made to verify the notes recorded in the charts.

Radiographic Review

The radiographs of the bony thorax in this series of children were reviewed. The pertinent radiographs of all

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TABLE I. Characteristics of Children in This Study

Characteristic	Number (%)
Males	67 (47.5)
Mean age at diagnosis, months (range)	22.6 (0–168)
Alive at time of chart review	102 (72.3)
Stage of tumor	
1	33 (23.4)
2	13 (9.2)
3	34 (24.1)
4	45 (31.9)
4s	16 (11.3)
Ethnic group	
French-Canadian	131 (92.9)
others[a]	10 (7.09)
Congenital abnormalities	
children	12 (8.5)
abnormalities	21

[a]Four were of East Asian origin, two Middle Eastern, one Italian, one Colombian, and two were of mixed ancestry. One out of the 12 children who had congenital anomalies was of Chinese-Cambodian descent. All others were French-Canadian.

141 children were sought. Nearly all children at St. Justine Hospital with neuroblastoma diagnosed in the relevant time period had a skeletal survey performed. In order to view the entire bony thorax, it is necessary to have abdominal views, as a standard chest radiograph may miss anomalies of the last two sets of ribs. Radiographs of sufficient quality were available from 131 of the 141 children (92.9%). They were all reviewed by one observer (D.F.) over a 3-month period in 1996. The reviewer was blinded to the clinical details of the patients at the time of review. No control radiographs were reviewed as it was not possible to find a sufficient number of children without cancer who had undergone a skeletal survey; a plain chest radiograph would be likely to miss abnormalities of the twelfth and possibly eleventh ribs.

Statistical Methods

The observed numbers of malformations were compared with expected numbers from the British Columbia Health Surveillance Registry (a description of this resource is provided by Baird) [18]. The significance of differences seen between these two sets of figures was assessed assuming a Poisson distribution of events. The means of the ages at diagnosis of neuroblastoma in the different subgroups were compared for significant differences using a *t*-test on log-transformed data.

The British Columbia Health Surveillance Registry (HSR)

The British Columbia HSR compiles data on the number and type of all malformations for children born in British Columbia, according to the ICD classification scheme. It was established in 1952 in the Division of Vital Statistics of the Provincial Ministry of Health [18]. Information is derived from >60 types of record source, and there is no age limitation on when such abnormalities can be registered. The source records include the physician's notice of birth, the hospital admission and discharge forms, voluntary agencies, and death certifications. Although information is recorded for stillbirths, the present analysis is restricted to liveborn children. The children used for this comparison were born in British Columbia between 1979 and 1988. There were a total of 419,646 births, and 25,661 reported malformations among 18,643 children in British Columbia during this period. As has been stated by Baird [18], no adjustment is made for under-ascertainment, outmigration, etc.

RESULTS

Details of the children included in this study are shown in Table I. Nearly all the children were of French-Canadian descent (92.9%). More than three-quarters of the cases were stage 2 or greater at time of diagnosis. Other characteristics not shown in Table I were not strikingly different from expected results, and there was no excess of twinning (one dizygotic twin and one monozygotic twin out of 103 children where the information was recorded). Neither of the two co-twins were affected by neuroblastoma at the time of chart review. There was no clear deficiency or excess of premature births (two children were born before 36 weeks, at 34 and 35 weeks. Data were missing, however, on 73 (51.8%) of the children). The average age of the father was 34.5 years (range 20–51), and the mother, 28.4 years (range 19–45). These figures are based on records obtainable in 88 and 89 children, respectively. There were no cases of familial neuroblastoma (i.e., more than one affected individual in a family), and there were no striking features or excesses of the illnesses recorded in the charts that were attributed to the parents and/or their families. One child was reported to have a sister with leukemia, but no other childhood cancers were seen in the siblings of these children.

There were 21 defined abnormalities in 12 children. The anomalies seen in these 12 children are shown in Tables II and III. These frequencies were compared to the British Columbia Health Surveillance Registry (BCHSR) data on congenital malformations, and the frequency of malformations in this series was found to be significantly in excess of that expected from the registry data (for all malformations, RR: 1.91, $P = 0.03$). However, if the two children with rib abnormalities are excluded, the excess is no longer significant (RR $= 1.60$, $P = 0.11$). There was, however, a highly significant excess of cardiovascular, gastrointestinal, bony thorax, and renal abnormalities (Table II). In addition to the 12 children, nine children had questionable abnormalities that were excluded from the total. One child had left ventricular hypertrophy at age 15, but an echocardiogram performed

TABLE II. Twenty-one Congenital Abnormalities Reported in 12 Children With Any Congenital Malformation

ICD code	Abnormality	No. of children affected[a]	Expected (B.C.)[b]
7410	spina bifida cystica, with hydrocephalus	1	0.0497*
745–747	**Heart and circulatory system**	**6**	**1.75****
745	septal defects	4	0.618**
7459	atrial septal defect (unspecified)	1	0.0170*
7454	ventricular septal defect	1	0.287
7455	ostium secundum type	2	0.287
7460	pulmonary valve stenosis	2	0.0596**
7468	other specified heart defects (dextrocardia)	1	0.105
7470	patent ductus arteriosus	2	0.456
750–751	**Upper alimentary and digestive system abnormalities**	**4**	**0.731****
7503	tracheo-esophageal fistula with esophageal atresia	1	0.0426*
7505	pyloric stenosis	1	0.237
7510	Meckel diverticulum	1	0.213
7512	anal imperforation	1	0.0511
7514	intestinal malrotation	1	0.0355*
	Other anomalies		
7528	phimosis	1	0.277
7530	renal agenesis (unilateral)	2	0.0568**
7563	rib and sternum abnormalities	2	0.00994****
7580	Down syndrome	1	0.143
	Total	21	8.82***

[a]Numbers in bold correspond to the total number of children in this classification of abnormality and are not the sum of numbers in plain type. The numbers in plain type are the total number of children with the individual type of malformation reported. The only rib and sternal abnormalities included here were bifid ribs and extra ribs (one child in each category). See Results for explanation.

[b]British Columbia Health Surveillance Registry of congenital defects in live-born children (rates given per 10,000 children for the years 1979–1988, multiplied by 141).

*P = 0.05 to 0.01, **P < 0.01, ***P < 0.001, ****P < 0.001.

1 month earlier had been at the upper limit of normal. Another child had a patent ductus arteriosus (1 mm in diameter) diagnosed only at autopsy at age 7 weeks. Three children had cardiac abnormalities that were not present on repeat investigation (or confirmatory investigations were not available); one child had a congenital hemiparesis and another, diagnosed at 21 months of age, was found to have a ''strange face'' with a flat, broad nose, a high arched palate, and right internal strabismus and hyperteleorism. No definitive diagnosis was recorded in the chart, but fragile X was excluded at age 4. Interestingly, both parents had a hearing disability and the child's older brother was born with cleft lip and palate. One child had sinus bradycardia and another internal bilateral tibial torsion, which is regarded as an intrauterine positional defect.

It is interesting to note that the average age of diagnosis of neuroblastoma was 22.6 months overall (Table I) and 23.4 months in children without malformations. By contrast, the average age of diagnosis in those with congenital anomalies was 12.5 months (Table III). However, the difference in mean age of diagnosis of neuroblastoma in those with (n = 12) and without malformations (n = 129) is not significant ($P > 0.05$). The trend toward a younger than average age of diagnosis in the subgroup with congenital abnormalities (n = 12) is probably not explained by increased vigilance in those with congenital anomalies, as the age of diagnosis of neuroblastoma in children where the congenital anomalies were noted first (n = 10) was 13.3 months, whereas in two children where the neuroblastoma was diagnosed before the congenital anomaly, the average age of diagnosis was 7.5 months. However, this difference is also not significant.

The review of the bony thorax radiographs of 131 children revealed that 23 children (17.6%) had some type of anomaly or variant (Table IV). The most common anomaly was hypoplasia of the 12th rib (11 cases, of which 8 were bilateral). No child had a cervical rib. Two children also had some type of other congenital anomaly. One is child 113 in Table III, and the other was not included in the totals because follow-up investigations were not recorded in the charts (although a patent ductus arteriosus was present at 2 days of age). Although abnormalities of the twelfth rib were common, they were not included in Tables II or III. This is because it is unlikely that these anomalies would be detected on standard chest radiographs and therefore cannot be compared with expected rates from a registry. Bifid or addition ribs should be detected, so two children with these anomalies are recorded in Table II. In addition to these findings, 13 children had rib erosions secondary to thoracic neuroblastoma. These children were excluded from the totals.

DISCUSSION

Congenital Anomalies and Neuroblastoma

The mean age at diagnosis and stage range of these children is similar to that reported by others [19,20]. There was no excess of male cases as has been reported by previous authors [20]. The most striking result of this study is the excess of congenital anomalies. The results presented here together with several previous studies summarised in Table V, indicate that there may be a relationship between neuroblastoma and congenital malformations. It is of special note that there does not appear to be a specific syndrome associated with neuroblastoma. However, excesses of cardiovascular, skeletal, or gastrointestinal abnormalities have been seen in other series [5,12] and in the present study. In addition, there are numerous case reports of the association between congenital anomalies and neuroblastoma [4,6–9,21]. Within

TABLE III. Clinical Descriptions of the 12 Children With Neuroblastoma and Congenital Abnormalities*

Child number	Congenital abnormalities	Neuroblastoma	Age of diagnosis (months)	Outcome
6	Ventricular septal defect	stage 1, thoracic	21	alive
23	Spina bifida with hydrocephalus	stage 3, intraabdominal	55	alive
34	Meckel diverticulum	stage 4, left adrenal	7	alive
69	Patent ductus arteriosus	stage 3, right adrenal	19	alive
77	Down syndrome, single common Atrioventricular cavity (de Rastelli)	stage 3, left adrenal	15	alive
88	Phimosis	stage 4s, thoracic	3	alive
90	Pulmonary valve stenosis	stage 3, intrathoracic	6 (via screening)	alive
91	Pyloric stenosis	stage 1, right adrenal	1.5	alive
104	Intestinal malrotation, unilateral renal agenesis	stage 1, right adrenal	5	alive
113	Ostium secundum atrial septal defect	stage 4s, right adrenal	12	alive
119	Esophageal atresia, imperforate anus, absent right kidney, tracheo-esophageal fistula, dextrocardia, atrial septal defect	stage 4s, left adrenal	4	alive
131	Patent ductus arteriosus, ostium secundum atrial septal defect, pulmonary valve stenosis	stage 4, retroperitoneal	2 (via screening at 3 weeks}	alive

*Excluding the children with rib abnormalities: see Materials and Methods.

TABLE IV. Rib Abnormalities in Children With Neuroblastoma

Abnormality	No. of children affected (n = 131)[b]	Other congenital abnormalities in children with rib abnormalities
Absence of 12th rib[a]	10	2
Unilateral	2	nil
Bilateral	8	2: one child with mild hemihypertrophy, patent ductus arteriosus and left ventricular hypertrophy; the other is case 113 in Table 2 (ostium secundum defect)
Hypoplasia of 12th rib[a]	11	nil
Unilateral	3	—
Bilateral	8	—
Bifid ribs	1[c]	nil
13 ribs	1	nil
Totals	23/131 (17.5%)	2/23 (8.7%)

[a]Not included in Tables II or III; see Results for explanation.
[b]Radiographs were missing, or were not possible to interpret in 10 children.
[c]Three bifid ribs on right, one on left.

these broad categories, there are many different disorders; thus it is more likely that neuroblastoma and congenital malformations are the varying expression of a common diathesis than that they have a causal relationship. The variation in the results from different series is also quite striking, and may point to specific environmental causes (see below).

There also have been reports supporting an association between congenital anomalies and other childhood cancers, in particular Wilms' tumor, soft tissue sarcomas, Ewing sarcoma, hepatoblastoma, and germ cell tumors [12,22–25]. None of these tumors is known to have a large hereditary component. Of note was the finding of Yang et al. [22] that six of 15 children with major birth defects and rhabdomyosarcoma had both conditions in the same region of the body. Local effects could be excluded in at least three of the six cases. However, these findings were not supported in a study from the Manchester Children's Tumour Registry [23]. In a comparable study of numerous types of childhood cancer, there was an excess of minor (but not major) anomalies in 106 affected children compared with the same number of age, sex, and ethnicity-matched controls [26]. Of note was the excess of minor anomalies in the sibs of cases: 69.2% of cases, 63.0% of sibs, and 34.6% of control children had one or more minor anomaly. Only four children were affected by neuroblastoma.

Sources of Bias

This study has several possible sources of bias. Because many of the children received chemotherapy, it is possible that their malformations were detected only because they had investigations before starting chemotherapy. However, in 10 out of the 12 cases, the neuroblastoma was diagnosed after the congenital malformations were noted. Second, as St. Justine is a referral center for childhood cancers, there may have been ascertainment bias, in that cases with malformations and cancer may have been preferentially referred to this hospital. As far as can be established, no child in this study was referred to St. Justine because of a congenital malformation. It is also noteworthy that previous studies studying the incidence of congenital malformations in children with neuroblastoma may have particularly underestimated the incidence of cardiovascular malformations as

TABLE V. Review of Evaluable Data on Congenital Malformations and Neuroblastoma

Study group	Findings	Risk of neuroblastoma/ congenital malformations	Reference
1,208 children with cancer in UK National registry of childhood tumors, 1971–1986	Overall, no excess of malformations. On subanalysis: 9 cases of gastrointestinal malformations, 3.74 expected; 5 observed cases of spine and rib abnormalities, 0.35 expected.	$P > 0.05$ $P < 0.05$ $P < 0.001$	(12)
32 children with neuroblastoma treated at the University of Rochester medical center between 1965–1980	3 children had congenital anomalies; XII nerve palsy (possibly a local effect), plagiocephaly type C, capillary hemangiomata.	—	(9)
97 children with neuroblastoma with matching birth certificates identified at the Mayo Clinic, 1968–1987	2 children had congenital anomalies: meningomyelocele and microcephaly, hydrocele.	Not significant	(44)
504 children diagnosed with neuroblastoma in U.S. centers 1941–1964, who had hospital charts for review	54 children had a congenital malformation, 10 had another tumor. There was no specific excess, but no comparisons were available. Skull or brain abnormalities were considered to be overrepresented.	—	(13)
37 children with neuroblastoma registered with the Tokyo Metropolitan Area Childhood Cancer Registry, 1966–1968	13 children had congenital anomalies (35%), 6 children had major anomalies, and 7 had minor anomalies (such as abnormal dermatoglyphics).	—	(10)
35 children with neuroblastoma living in three health authority regions of England.	4 children had congenital anomalies; 4 matched control children were also affected.	Not significant	(14)
19,373 children with birth defects diagnosed at <12 months, born in Atlanta, GA, 1968–1987	In children with birth defects, the cumulative incidence of neuroblastoma was 0.32; for all births it was 0.02 (abnormalities seen: patent ductus arteriosus, vesico-ureteric reflux, pyloric stenosis, cystic nephroma, hydrocephalus, inguinal hernia).	20.3 (95%CI: 5.5–52.1)	(11)
10,891 children with birth defects diagnosed at <12 months, Iowa, 1983–1989	In children with birth defects, the cumulative incidence of neuroblastoma was 0.26; for all births it was 0.12 (abnormalities seen: congenital hip dislocation, ostium secundum defect).	2.2 (95%CI: 0.3–7.9)	(15)
144 cases of neuroblastoma at Great Ormond Street	5 children had congenital anomalies: ventricular septal defect, anomalous aortic arch, congenital dislocation of the hip, bilateral pes cavus, pyloric stenosis.	Null hypothesis not rejected, $P = 0.35$	(16)
22,856 Norwegian children with congenital malformations, born 1967–1980	2 children developed neuroblastoma, giving a rate of 1.4 per 100,000 person-years.	1.1 (95%CI: 0.4–3.4)	(17)
88 children with neuroblastoma at one University Children's Hospital in Germany	33% had cervical ribs, and rib bifurcation was significantly in excess.	—	(5)

echo-cardiography may not have been performed. It is also possible that the number of congenital anomalies noted in the British Columbia Health Surveillance Registry are an underestimation of the congenital anomalies in the community; this would artificially elevate the significance of our findings. For example, abnormalities of the bony thorax may be more common in the general population than is suggested by registry data [27]. In general, the wide scope of the reporting system of the registry and the consistent recording of birth defects since 1966 [18] will limit this effect for many abnormalities that are noted in neonates and infants. Underascertainment is as likely to be present in our series as in the BCHSR. However, a previous report of an excess of congenital malformations in an autopsy study of rhabdomyosarcoma [24], which was not in agreement with other studies based on chart review or physical exam [10,23] demonstrates some of the difficulties in establishing the correct control group, and it is possible that our study is also subject to this error. It is also possible that there is an

increased incidence of abnormalities in French-Canadian compared with other Canadian children, and we have not been able to address that possibility in this report.

Familial Neuroblastoma and Genetic Models of Neuroblastoma Formation

It has been suggested that like retinoblastoma, the occurrence of neuroblastoma can be explained by the ''two hit'' hypothesis and that hereditary cases of neuroblastoma accounted for 20% of the total number of cases [2,28]. Spontaneous regression of disseminated tumors is a special characteristic of neuroblastoma. This clinical entity is referred to as stage 4s neuroblastoma, whereas the more common disseminated form is designated stage 4. The regression seen in stage 4s neuroblastoma has been interpreted to mean that the lesions of stage 4s neuroblastoma are not actually cancers, but are nonmalignant lesions that have had ''one hit'' only and can therefore regress [29]. A competing hypothesis states that spontaneous regression occurs because ''the developmental time-switch for apoptosis is delayed'' [30]. This suggestion of a possible link between development control mechanisms and neuroblastoma is supported by some experimental data [31].

Although families with neuroblastoma have been reported, they are not common. Of 232 Danish children with neuroblastoma diagnosed between 1943 and 1980, one had neuroblastoma and neurofibromatosis (supporting the concept of neurocristopathy) [32], and one child had a sister with neuroblastoma and a mother with ganglioneuroblastoma at two sites [33]. These were the only two cases in this series that could be described as ''hereditary.'' It has been estimated that the risk to siblings and offspring of neuroblastoma cases is <6% (34) and that the heritable fraction of this cancer is <1% (3). The absence of neuroblastoma in the offspring of cases also supports these estimations [35–37].

Concordance in identical twins has been rarely reported [13,38], and there was no excess of neuroblastoma among 14,504 Norwegian twins [17]. The only monozygotic twin seen in our series had an unaffected co-twin, and we did not find any hereditary or familial cases. Additionally, there were no striking patterns of disorders reported in the relatives of the affected children. Taken together with previous data, this study suggests that the heritable fraction of neuroblastoma is low and that neuroblastoma does not fit the classical ''two hit'' model of retinoblastoma.

Developmental Genetics: Neuroblastoma and Congenital Malformations

Disruption of genes that encode transcription factors controlling morphogenesis, such as the PAX, HOX, and membrane tyrosine kinase families of genes, have been associated with a numerous abnormalities. The PAX family is particularly interesting, as germ-line disruption of PAX3 can result in Waardenburg syndrome, whereas a t(2;13(q35;q14) translocation, rearranging this gene and placing it adjacent to the forkhead gene (FKHR), is commonly seen in alveolar rhabdomyosarcoma. It is intriguing that PAX7 maps to 1p36.2, a region commonly deleted, or demonstrating loss of heterozygosity, in neuroblastoma [1]. PAX7 encodes a complete homeodomain and is also translocated to the same FKHR gene in a subset of alveolar rhabdomyosarcomas. The normal function of PAX7 is unknown. Other PAX genes are involved in eye and kidney development, as well as Wilms' tumor, glioblastoma, and thyroid cancer [39].

Some proto-oncogenes, such as the membrane-bound tyrosine kinase receptor RET, have dual roles in both cancer and development. RET is mutated in multiple endocrine neoplasia type 2 (MEN2) and its variants, and also in some cases of Hirschsprung's disease [40]. This latter disorder has been associated with neuroblastoma [41,42]. RON is another attractive candidate as it is a tyrosine kinase receptor expressed in epithelial, bone and neuroendocrine tissues. Its ligand is Macrophage Stimulating Protein (MSP), which despite its name can act as a mitogen in cell lines derived from tissues where it is expressed. In the neuroendocrine cell line PC12, proliferation resulted after adding MSP (43). RON has yet to be associated with either developmental defects or cancer. It will be of interest to study the effects of activating or disrupting these genes in laboratory animals. As yet, there are no in-bred mouse strains that spontaneously develop neuroblastoma (J. Nadeau, pers. comm.).

Environmental Agents Connecting Neuroblastoma and Malformations

A causal connection between malformations and childhood cancer could be via the maternofetal environment. Several studies have considered possible pre- and preinatal risk factors [44,45], but only frequent maternal alcohol consumption in pregnancy appeared to be a significant risk factor for neuroblastoma (odds ratio 9.0, 90% confidence intervals 2.16–37.6), when compared with telephoned controls [45]. It is interesting that heavy maternal alcohol consumption also can cause congenital malformations [46]. We did not have records pertaining to alcohol consumption in the parents of our cases. As this study was restricted geographically and ethnically, it may be worthwhile to consider other relevant environmental agents that might be implicated in both teratogenesis and carcinogenesis.

Conclusions

This study has shown a significant excess of congenital malformations in mainly French-Canadian children diagnosed with neuroblastoma at one Montréal hospital between 1977 and 1993. This finding is supported by

several studies, although most have shown no significant excess. There may be common underlying causes for neuroblastoma and some congenital anomalies. Genes that control morphogenesis and environmental agents that are both teratogenic and carcinogenic are worthy of further study in these children. We would concur with Sy and Edmonson [6] that ''most cases of neuroblastoma result from sporadic postzygotic disorders which at times may be teratogenic in the more classical sense.''

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